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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/694,190

10/28/2003

Lloyd Wolfenbarger JR.

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EXAMINER

FORD, ALLISON M

ART UNIT

PAPER NUMBER

1651

MAIL DATE

DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/694,190	<b>Applicant(s)</b> WOLFINBARGER ET AL.	
	<b>Examiner</b> ALLISON M. FORD	<b>Art Unit</b> 1651	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 04 January 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-7, 9-16, 19-27 and 29-67 is/are pending in the application.
- 4a) Of the above claim(s) 47-66 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9-16, 19-27, 29-46 and 67 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)<br>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)<br>3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____. | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date _____.<br>5) <input type="checkbox"/> Notice of Informal Patent Application<br>6) <input type="checkbox"/> Other: _____. |
|---|---|

## **DETAILED ACTION**

### ***Status of Application***

Applicants' petition for revival under 37 CFR 1.137(b) was granted on 7/31/2008. The reply of 1/4/2008, submitted with the petition, has been entered.

Claims 1, 2, 4, 14-16, 19 and 29-31 have been amended; claims 8, 17, 18 and 28 have been cancelled; claim 67 has been added as new. Claims 47-66 stand withdrawn as being directed to a non-elected invention pursuant to 37 CFR 1.142(b), election was made without traverse on 11/6/2006.

Claims 1-7, 9-16, 19-27 and 29-67 remain pending in the current application, claims 1-7, 9-16, 19-27, 29-46 and 67 have been considered on the merits.

### ***Priority***

Acknowledgement is made of applicants claim for priority under 35 USC 120 as a continuation-in-part to prior filed application 09/660,422 (filed 12 September 2000), now US Patent 6,743,574.

However, it is noted that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120, as discussed in the previous office action.

The effective filing date, for purposes of determining patentability, of the instantly claimed subject matter is considered to the filing date of the instant application: 28 October 2003.

### ***Response to Arguments/Amendments***

Applicants' arguments submitted 1/4/2008 have been fully considered, in combination with the amendments to the claims the previous grounds of rejection have been withdrawn. However, new grounds of rejection are set forth over Atala (US Patent 6,376,244), Wolfinbarger, Jr (US Patent 6,024,735), and Wolfinbarger, Jr (US Patent 6,432,712).

***Oath/Declaration***

The supplemental declaration, submitted 1/4/2008, cannot be accepted because it changes the name of one or more inventors without the proper petition under 37 CFR 1.182, and fee required therewith.

Therefore, the objection to the original declaration, submitted 10/28/2003, remains. Specifically, the current declaration appears to be that from parent application 09/660,422 (now US Patent 6,743,574), however, because the instant application is a continuation-in-part of the parent application, a new oath or declaration is required, pursuant to 37 CFR 1.67(e). The Application Data Sheet is not sufficient to negate the need for the oath or declaration in a continuation-in-part application.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 1-7, 9-16, 19-27, 29-46 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claims 1 and 2 remain rejected because it is unclear if the water is pass through a bed of hydrophobic adsorbent resin and anion exchange resin *prior* to use for washing the tissue, or *after*. Note the current claim language says: "...washing at least some cell lysis remnants from said extracted tissue to remove the cell lysis remnants in the wash water..." It appears the underlined portion should refer to the extracted tissue, not the wash water. All claims inherent this deficiency, and thus are rejected on the same grounds.

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Claim 4 is rejected because it is not clear how a hydrophobic resin or a hydrophilic resin is used to remove at least one non-denaturing detergent. First, it is not clear what the at least one non-denaturing detergent is being removed *from* (as independent claims 1 and 2 no longer recite use of a 'non-denaturing detergent'). Second, it is not clear how a resin would effectively remove detergent from a solid tissue graft. Clarification is required.

Claims 29-31 depend from cancelled claim 28, and are therefore considered indefinite. Correction is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

**Claims 1-4, 12-16, 19-27, 29-46 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala (US Patent 6,376,244), in view of Wolfinbarger, Jr (US Patent 6,024,735).**

Atala disclose a process for decellularizing soft tissue organs for subsequent implantation into a mammalian system.

The method of Atala comprises mechanically agitating an isolated organ to disrupt cell membranes;

treating the mechanically agitated, isolated organ in a solubilizing fluid to extract cellular material from the organ (which Applicants call "extracting a soft tissue sample with an extracting solution") to produce an extracted organ;

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washing the extracted organ in a washing fluid to remove cellular debris, to produce a substantially decellularized organ; and optionally

equilibrilizing the substantially decellularized organ in equilibrilizing fluid (which reads on a storing step) (See Atala, col. 2, ln 43-67).

Atala states the solubilizing fluid (which is considered to read on the extracting solution of the current claims) may be an alkaline solution having a detergent. A variety of detergents are disclosed, including sodium cholate and deoxycholates (See Atala, col. 3, ln 14-30). In Example 1 Atala carry out the solubilization (extraction) step at a temperature of 4°C (See Atala, col. 9, ln 55-65).

Atala states the washing fluid may be distilled water, physiological buffer or culture medium (See col. 3, ln 31-34). The distilled water used by Atala is considered to be chemically identical to water which has been passed through a bed of hydrophobic adsorbent resin and anion exchange resin (as required by the current claims), as both waters are free of impurities. The step of processing the water prior to use is considered to be a product-by-process limitation. Product-by-process limitations are considered only insofar as the method of production imparts distinct structural or chemical characteristics or properties to the product. Therefore if the product, as claimed, is the same or obvious over a product of the prior art (*i.e.* is not structurally or chemically distinct), the claim is considered unpatentable over the prior art, even though the prior art product is made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

Atala state the equilibrilizing solution (considered to read on the storage solution of the current claims) may comprise distilled water, physiological buffer and culture media (See Atala, col. 2, ln 64-67). Each of distilled water, physiological buffer and culture media are considered to read on water replacement agents.

It is noted that the method of Atala is reported to *substantially* decellularize the organ (See Atala, col. 2, ln 59-63 & claim 1); as such it is a reasonable interpretation that at least some cell lysis remnants remain in the final product. These cell lysis remnants are considered to read on "cellular elements capable of inducing graft repopulation with an appropriate cell type" as required by the instant inventions.

Atala differs from the method of the current claims in that they do not teach using pressure mediated flow of either the solubilizing fluid (extracting solution), washing fluid or the storage solution when preparing the organ. However, it is submitted that use of pressure mediated flow of the solutions was recognized as conventional in the art, at the time the invention was made (See Wolfinbarger, Jr), and thus application of such in the method of Atala would have been *prima facie* obvious. For example, Wolfinbarger, Jr disclose several recirculation methods whereby solutions are flushed through a graft material using positive and negative pressure (See Wolfinbarger, Jr, col. 13, ln 6-col. 19, ln 36). One of ordinary skill would have had a reasonable expectation of successfully applying the pressure mediated recirculation methods of Wolfinbarger, Jr to the process of Atala because the pressure mediated recirculation methods of Wolfinbarger, Jr involve simple mechanics of applying positive and negative pressures to fluids to flush a material. The pressure mediated flow and recirculation methods could have routinely been applied to either, or all of, the solubilizing fluid (extracting solution), washing solution or the storage solution of Atala. (claims 1-4, 13-15, 21, 22, 26, 43, 44)

Some of the parameters and conditions required by the instant claims are not specifically disclosed by Atala or Wolfinbarger, Jr, specifically the concentration/amount of the detergent used in the solubilizing (extracting) fluid of Atala, the duration of the solubilizing (extracting) step, the temperature at which the solubilizing (extraction) is to be carried out, or the flow rate of the pressure mediated flow;

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however each of these parameters are recognized as result effective variables that directly affect the degree to which the organ is decellularized, and the extent to which the native structure of the matrix is retained. As result effective variables, each of these parameters would have been routinely optimized by one of ordinary skill in the art at the time the invention was made. "[W]here the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation" See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to the conditions under which the solubilizing (extracting) step is carried out, Atala states the concentration of detergent in the solubilizing fluid is a result effective variable, and would be varied based on the tissue being treated (See Atala, col. 6, ln 48-58 & col. 7, ln 18-31). The concentration of a particular detergent would be routinely optimized by one of ordinary skill in the art in order to achieve the desired result of effectively removing cellular components, without disrupting the interstitial structure of the organ. It logically follows that the duration of the solubilization step (extracting step) would be recognized as a result effective variable that, too, would have been routinely optimized by one of ordinary skill in the art at the time the invention was made. (claims 29-33, 39-42, 45, 46)

With regards to the flow rate of the pressure mediated flow, Wolfinbarger, Jr further state the flow rate of the pressure mediated flow is a result effective variables (See Wolfinbarger, Jr col. 13, ln 53-col. 14, ln 6). The flow rate directly affects the extent of removal of cellular debris, as well as the extent of damage caused to the matrix structure. (claims 35-38)

The method of Atala further differs from the method of the current claims in that they do not teach including a decontaminating agents in the solubilizing (extracting) solution or in the storage solution. However, Wolfinbarger, Jr teach including decontaminating agents in detergent solutions intended to remove cellular lysis remnants from tissues and in storage solutions for storing decellularized



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tissues intended for subsequent use in implantation procedures to improve sterility. The decontaminating agent may be one or more of antibiotics, antiviral agents or hydrogen peroxide (See Wolfinbarger, Jr, col. 11, ln 37-47 & col. 22, ln 53-55). Other suitable decontaminating agents, as well as appropriate concentrations, would be readily recognized by one of ordinary skill in the art (claims 19, 20, 23-25, 34, 67)

It is further noted, to improve sterility and reduce contamination, Wolfinbarger, Jr suggest use of endotoxin-free, deionized/distilled water (See Wolfinbarger, Jr col. 6, ln 1-2). One of ordinary skill in the art would have recognized the desirability of using USP grade, ultrapure, endotoxin free water for applications wherein the product is intended for implantation into mammalian systems, and thus use of such water would have been *prima facie* obvious in the method of Atala. (claims 16 and 22).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

**Claims 1-7, 9-16, 19-27, 29-46 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala (US Patent 6,376,244), in view of Wolfinbarger, Jr (US Patent 6,024,735), and further in view of Wolfinbarger, Jr (US Patent 6,432,712).**

The teachings of Atala and Wolfinbarger, Jr ('735) have been set forth in detail above. Neither Atala nor Wolfinbarger, Jr ('735) disclose including an endonuclease in the solubilizing (extracting) solution. However, Wolfinbarger, Jr ('712) discloses using a broad spectrum, recombinant endonuclease BENZONASE<sup>TM</sup> to decellularize organs and tissues (See Wolfinbarger, Jr ('712), col. 8, ln 40-67). Because the method of Atala is intended to result in a decellularized organ, it would have been *prima facie* obvious to one of ordinary skill in the art to include BENZONASE<sup>TM</sup> in the solution intended

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to remove cellular components from the organ. One would have had a reasonable expectation of successfully including BENZONASE, and determining an appropriate concentration, based on the teachings of Wolfinbarger, Jr ('712). (claims 5-7 and 9-11).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Double Patenting***

Applicants submitted a terminal disclaimer (1/4/2008) to overcome the double patenting rejection over commonly owned US Patent 6,743,574. The terminal disclaimer has been reviewed and was accepted.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/  
Primary Examiner, Art Unit 1651